

Remarks/Arguments

Claims 1 to 22 are pending. Claims 1 and 2 have been amended. New Claims 19 to 22 have been added and are supported by original Claim 1.

The Office Action stated: that applicants' election of species B in the reply filed on 2/5/08 is acknowledged, because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)); that applicants' response is entirely directed to paraphrasing restriction requirement; that applicants have not directed any argument against the content of the restriction itself; and that, however, upon further consideration, the species election is withdrawn and all of the claims will be examined. Applicants point out that the Examiner's position is incorrect because the restriction itself was in error for not complying with the requirements therefor, and that, in such a situation, there does not have to be an argument against the content of the restriction requirement because the very restriction requirement itself was in error. Also, applicants point out that the process of imposing a restriction requirement and then withdrawing it imposes a burden and cost on applicants that was unnecessary.

The Office Action stated that Claims 1 to 18 (now 1 to 22) have been presented for examination.

The following is a quotation of 35 U.S.C, 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if differences between subject matter sought to be patented and prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The Office Action stated: that this application currently names joint inventors; and that, in considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary; and that applicants are advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 to 18 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Omura et al. (U.S. Patent No. 4,107,297: cited in the IDS filed 1/4/08) in view of Hershberger et al. (U.S. Patent No. 4,637,981), Borghi et al. (U.S. Patent No. 5,135,857) and Nabais (1995). Applicants traverse this rejection.

The Office Action states that Omura et al. discloses the recovery of staurosporine (AM-2282) from a fermentation broth. Applicants traverse this statement because Omura et al. does not make such a generic statement. The Examiner has incorrectly attempted to generify the limited disclosure of Omura et al.

The Office Action stated that, for example, a fermentation broth containing staurosporine can be separated into microbial bodies and filtrate by filtration or without separating the broth into solids and liquid. Note that applicants' Claim 1 requires ultrafiltration.

The Office Action stated that the latter method is based on the physical [and] chemical characteristics of staurosporine which is fat-soluble. This statement is part of the very basis why one ordinarily skilled in the art would read Omura et al. and then discard it in the quest for applicants' claimed invention. Omura et al. states:

"...AM-2282 is soluble in fat." [col. 6, line 47]

It is this fact that would drive one ordinarily skilled in the art away from Omura et al.

Omura et al. also states:

"The ethyl acetate layer was concentrated under reduced pressure to give brownish coagulant (about 1.3 g) which was washed with ethyl ether (50 ml) to remove fatty impurities." [col 7, lines 41 to 44]

Does this mean that some AM-2282 was in or bound with such fatty impurities and lost when the latter was removed. The loss of product is reason to avoid Omura et al.

Omura et al. states that AM-2282 is sparingly soluble in ethyl acetate.

The Office Action stated that Omura et al. provides an example wherein a culture broth is adjusted to pH 10 and extracted with butyl acetate. Omura et al. states that AM-2282 is sparingly soluble in butyl acetate.

The Office Action stated that, the extract is concentrated in vacuo to a small volume and transferred into water at pH 10. Accordingly, Omura et al. would teach that extraction of AM-2282 would be poor because AM-2282 was sparingly soluble in butyl acetate, and hence one ordinarily skilled in the art would be directed away from the use of Omura et al. in the search for the claimed invention.

The Office Action stated that the aqueous mixture is extracted with ethyl acetate. Omura et al. extracts AM-2282 from water using ethyl acetate, which directs away from applicants' use of a mixture of water and ethyl acetate (or other organic solvent B) to extract from the retentate of the diafiltrating. This shows the unobviousness of Claims 6, 11 to 13 and 18.

The Office Action stated that the organic layer is evaporated to obtain the product and then chromatographed in silica gel (col.6, lines 40 to 60). This does not make applicants' process obvious.

The Office Action stated that the crude product is recrystallized to provide pale yellow needles (col. 7, lines 1 to 4: as in Claim 17). This does not make applicants'

claimed invention as a whole obvious.

The Office Action stated that Omura et al. states that staurosporine recovery can be achieved by "known methods for separating antibiotics" (col. 6, lines 41 to 42). This statement of Omura et al. is so broad as to be meaningless under Section 103(a) and clearly would cover many of such process that would be inoperable re AM-2282 and applicants' claimed process.

The Office Action stated that Claims 2 to 11, 13, 14 and 18 are rejected because they limit steps that are indicated as optional in Claim 1. Applicants traverse this statement as it has no basis in law. The burden under Section 103(a) is on the Examiner and he has not cited any support in law for his position, hence the Examiner is left with Claims 2 to 11, 13, 14 and 18 being allowable. The Examiner has not shown otherwise.

The Office Action stated that, for the purposes of this rejection, these claims are interpreted that the optional steps are not performed. This interpretation has no support in logic or law. The term "optionally" means that there are two processes – one without the optional step included and one with the optional step included. The Examiner is requested to support his interpretation in practice or law, or to drop it. M.P.E.P., 2173.05(h)(III), states "...was considered acceptable alternative language because there was no ambiguity as to which alternatives were covered by the claim." The Examiner has not shown that any such ambiguity is present – he has the burden of proof.

The Office Action stated that Omura et al. does not disclose that staurosporine is recovered from a fermentation broth by diluting the broth with a water-miscible organic solvent, ultrafiltration of the diluted broth, concentration and adjustment of the pH to at least 8.5 to precipitate the product which is collected by the centrifugation. The Examiner has shown why Omura et al. is not a very relevant reference and why one ordinarily skilled in the art would discard Omura et al. in the hunt for applicants' claimed

invention.

Furthermore, the Examiner has not shown why one ordinarily skilled in the art would combine the three secondary rejection references with Omura et al. in the search for applicants' claimed invention. The burden is upon the Examiner to show why in the record or drop the obviousness rejection.

The Office Action stated that Hershberger et al. discloses that a broth containing a glycopeptide antibiotic, factor G, is diluted with a water miscible organic solvent such as acetone, acidified and filtered to separate the mycelium and other insolubles. Hershberger et al. directs one ordinarily skilled in the art away from applicants' claimed invention. The Examiner has stated that Hershberger et al. acidifies a broth/ water miscible organic solvent. Column 9, lines 37 to 58, of Hershberger discloses start at a pH of 1 to 2, filtering, moving the pH to 3 to 4, concentrating, and adjusting pH to 6.5 to 7 with the free base form antibody precipitating. Hershberger et al. directs one ordinarily skilled in the art away from applicants' claimed process. Applicants adjust the pH of their concentration to at least 8.5 (although adjusting to such pH before concentration). Hershberger is from very acidic at the start to neutral at the end (not into the basic at any time). To the contrary, applicants require that the concentration be moved into the basic, if not already there. All of the teachings of a reference and the prior art of record must be considered under Section 103(a). The teachings of the rejection references are in direct conflict, and the Examiner has no basis for choosing one conflicting teaching over the other, and conflicting teachings is no basis for a holding of obviousness (particularly where the level of ordinary skill in the art has not been determined).

The Office Action stated that the filtration can be accomplished with dichotomous earth or other commercially available filter aids. This does make applicants' claimed invention as a whole.

The Office Action stated that separation can also be accomplished by centrifugation. This does not make applicants' claimed invention obvious

The Office Action stated that, after separation, the liquid portion is evaporated to remove the solvent. This is of little relevance as Hershberger et al. is not a very relevant reference.

The Office Action stated that Hershberger et al. reports that the disclosed antibiotic, factor G, was separated on a resin and the eluate was precipitated as the free base at pH 6.5 to 7.5. Hershberger et al. directs away from the claimed invention

The Office Action stated that Hershberger et al. teaches that, alternatively, factor G can be recovered from the fermentation medium by conventional isolation procedures such as absorption on a suitable ion exchange resin followed by chromatographic separation (col. 9, lines 31 to 65). This does not show obviousness.

The Examiner has not shown that one ordinary skilled in the art would combine Hershberger et al. with the other rejection references in the search for applicants' claimed invention.

The Office Action stated that Nabais discloses that ultrafiltration is an effective method to separate the solids from a broth to effect the recovery of clavulanic acid (abstract).

The Office Action stated that Borghi et al. discloses that the antibiotic, teicoplanin, can be isolated from the extract of a mycelium by techniques known in the art including extraction with solvents, precipitation with nonsolvents or by changing the pH of the solution, partition chromatography, reverse phase chromatography, affinity chromatography and the like (col. 6, lines 50 to 57). This broad statement does not make applicants' invention as a whole obvious.

The Office Action stated that, thus, Borghi et al. establishes that methods for the recovery of antibiotics from biological sources are well established in the art. This

statement is so broad as to be vague and meaningless under Section 103(a).

This obvious rejection fails for not complying with the Supreme Court's Graham and KSR decisions and Patent Office policy. The Examiner has not determined, as is mandatory, in the record the level of ordinary skill in the art – without this mandatory factual determination, the Examiner cannot make any valid obviousness rejection. Also, accordingly, the Examiner cannot know any thing about one ordinarily skilled in the art. The Examiner has not factually shown in the record a case of prima facie obviousness (and the Examiner cannot until she complies with Graham, KSR and Patent Office policy on the matter).

The Office Action stated that it would have been obvious to one of ordinary skill in the art at the time the invention was made to recover staurosporine from a fermentation broth by diluting the broth with a water-miscible organic solvent, ultrafiltering and concentrating broth, and then adjusting the pH of the concentrate to at least 8.5 to precipitate and collect the product by centrifugation. Applicants traverse this statement. The Examiner does not know what would be obvious to one ordinarily skilled in the art. The Examiner still has the burden of proof.

Before moving on with the Office Action statements, the Examiner's use of the term "ordinary artisan" is meaningless under Section 103(a) because it is not the same as "the artisan ordinarily skilled in the art" ("one ordinarily skilled in the art") which is the standard required under Section 103(a). Wherever the Examiner has used such term, the statement is meaningless under Section 103(a).

The Examiner has cited a Board decision that is meaningless to this case. The Board decision deals with one ordinarily skilled in the art, but the Board decision (at least what has been quoted and described by the Examiner) did not deal with determining the level of ordinary skill in the art. The problem in the present situation is that the Examiner has not determined the level of ordinary skill in the art so the Examiner know nothing

about one ordinarily skilled in the art.

The Office Action stated that the ordinary artisan would have been motivated to do so because in *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int., 2007), the Board found that "when there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical group. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense". This statement and the quoted Board decision are not pertinent. The ordinary artisan is not relevant to Section 103(a). The cited Board decision is not relevant because it only deals with the situation where the level of ordinary skill in the art has already been determined.

The Office Action stated: that the case was directed to an isolated nucleic acid molecule; that the claim stated that nucleic acid encoded a particular polypeptide; that the encoded polypeptide was identified in the claim by its partially specified sequence, and by its ability to bind to a specified protein; that a prior art patent to Valiante taught the polypeptide encoded by the claimed nucleic acid, but did not disclose either the sequence of the polypeptide, or the claimed isolated nucleic acid molecule; that, however, Valiante did disclose that by employing conventional methods such as those disclosed by a prior art laboratory by Sambrook, the sequence of the polypeptide could be determined, and the nucleic acid molecule could be isolated; that, in view of Valiante's disclosure of the polypeptide, and of routine prior art methods for sequencing the polypeptide and isolating the nucleic acid molecule, the Board found that a person of ordinary skill in the art would have had a reasonable expectation that a nucleic acid molecule within the claimed scope could have been successfully obtained; that, relying on *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995), appellant argued that it was improper for the Office to use the polypeptide of the Valiante patent together with the methods described in Sambrook to reject a claim drawn to a specific nucleic acid

molecule without providing a reference showing or suggesting a structurally similar nucleic acid molecule; that, citing KSR, the Board stated that "when there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp; that, if this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."; that the Board noted that the problem facing those in the art was to isolate a specific nucleic acid, and there were a limited number of methods available to do so; that the Board concluded that the skilled artisan would have had reason to try these methods with the reasonable expectation that at least one would be successful; and that, thus, isolating the specific nucleic acid molecule claimed was "the product not of innovation but of ordinary skill and common sense." This Board is not relevant to this case because it does not deal with the determination of the level of ordinary skill in the art. Instead, the Board decision only deals with one ordinarily skilled in the art (that is, after the level of ordinary skill in the art has been determined). Patent Office policy and the Supreme Court decision require determination of the level of ordinary skill in the art as a mandatory prerequisite before a valid decision of obviousness can be made under Section 103(a). A claim is unobvious until, and only until, a valid showing of obviousness has been made by an Examiner (who has the burden of proof).

The Office Action stated that, in the instant case, the ordinary artisan would have recognized that there are a finite number of art-recognized solutions for the isolation of an antibiotic from a fermentation broth. This statement is meaningless because it is based on "the ordinary artisan".

The Office Action stated that Hershberger et al. discloses alternative methods for the initial treatment of the broth. As shown above, the acidic requirement of Hershberger destroys the obviousness rejection.

The Office Action stated that the dilution, filtration concentration steps taught by Hershberger et al. are conventional in the art and the ordinary artisan would have had a reasonable expectation that said would be at least comparable to the initial broth extraction steps employed by Omura et al. This statement is also meaningless under Section 103(a) because it is based upon "the ordinary artisan". The Examiner does not know what would be a reasonable expectation to one ordinarily skilled in the art. The acidic steps of Hershberger et al. eliminates this rejection.

The Office Action stated that, likewise, the ordinary artisan would have been motivated to substitute a method of changing the pH of the concentrate to precipitate staurosporine for the extraction/chromatography steps taught by Omura et al. because Borghi et al. established that said methods were well-known, finite, alternatives in the art of antibiotic isolation. The statement is also meaningless as it is based on "the ordinary artisan". Is the ordinary artisan fat, lean, tall, short, bald, long haired, flat footed, male, female, lazy, energetic, etc.?

The Office Action stated that, the ordinary artisan would have been motivated to employ a pH of least 8 or 10 (Claim 15) to precipitate staurosporine because staurosporine, like the glycopeptide taught by Borghi et al., would exist as a free amine at a basic pH and precipitate from the solution. It is of no meaning of what would motivate "the ordinary artisan". Applicants request that the standard required by Section 103(a) be used. Hershberger uses an acidic pH so there conflicting references and the teachings of non-relevant Borghi et al. is not controlling.

The Office Action stated that the ordinary artisan would have been motivated to employ ultrafiltration for the filtering step taught by Hershberger et al. because it is a commercially available filter aid that is conventional in the art for searing the insoluble material from a broth for the recovery of an antibiotic. The ordinary artisan has no relevance. The Examiner does not know what would motivate one ordinarily skilled in

the art.

The Office Action stated that the ordinary artisan would have had a reasonable expectation that he or she could successfully employ an ultrafiltration method to separate insolubles from a broth containing staurosporine because fermentation broths contain essentially the same components (e.g., proteins, microorganisms, small molecules, etc.). The ordinary artisan has no relevance. The Examiner know if one ordinarily has a reasonable expectation.

The Office Action stated that, therefore, the isolation of staurosporine from a fermentation broth is obvious because the field of antibiotic isolation from a broth is well developed and there a finite number of identified, predictable solutions that a person of ordinary skill would have good reason to pursue. Applicants traverse this statement. It is of no meaning to be “obvious” because the Examiner has not indicated to whom it would be obvious. The Examiner has not proven in the record, or identified, such finite number of identified, predictable solutions, or proven the they are predictable (to whom). The Examiner does not know what would be good reason to pursue to one ordinary skilled in the art.

The Office Action stated that the substitution of the known options to effect antibiotic purification are within the technical grasp of the ordinary artisan. This statement is meaningless under Section 103(a) as it is mere speculation and uses the false standard of the “ordinary artisan”.

The Office Action stated that, hence, the claimed method is not of one of innovation but of ordinary skill and common sense. This statement fails, for example, because the Examiner does not know what is ordinary skill in the art since she has not factually determined the level of ordinary skill in the art. So-called “ordinary skill” outside of the pertinent art is meaningless under Section 103(a). So-called “common sense” is not the standard under Section 103.

The claimed invention – which teaches inter alia the addition of a water-miscible organic solvent such as methanol, ethanol, propanol, 2-propanol, tert-butanol, acetone or tetrahydrofuran and the adjustment to a pH of at least 8.5 in a method to purify staurosporine – is not obvious in view of the (attempted) combination of references cited by the Examiner. Omura et al. teaches the use of n-butyl acetate, i.e., the use of a solvent which is only slightly soluble in water (0.7% at 20 °C) and not the use of a water-miscible organic solvent. Although Omura et al. states that staurosporine is only sparingly soluble in butyl acetate, there is no suggestion or motivation by Omura et al. to search for an alternative way of extracting staurosporine. Further, even though Hershberger et al. teaches the use of a water miscible organic solvent such as acetone for the isolation of an antibiotic, it should be noted that staurosporine and factor G, i.e., the antibiotic of Hershberger et al., are different molecules having different solubility in different solvents. Thus, it is questioned whether a method which functions to isolate one antibiotic is also applicable for the isolation of a different antibiotic. Further, applicants point out that Hershberger et al. does not describe the use of a water miscible organic solvent alone, but instead teaches a combination of using a water miscible organic solvent such as acetone and subsequently the acidification of the whole diluted fermentation broth. Thus, Hershberger et al. teaches away from applicants' claimed invention which claims adjustment to a pH of at least 8.5. In addition, it should be emphasized that a multi-step process for the isolation of staurosporine is claimed and that a prior art document which describes only one step of such multi-step process does not make the claimed invention multi-step process obvious to one ordinarily skilled in the art. Further, the attempted combination of rejection references directs away from applicants' claimed invention.

This rejection should be withdrawn.

A copy of the following references is enclosed:

1. Morioka et al., Agric. Biol. Chem., (1985), 49 (7), 1959-1963.
2. Oka et al., Agric. Biol. Chem., (1986), 50, 2723-2727.
3. Takahashi et al., Actinomycetologica, (1995), 19-26.
4. European Published Patent Application 0444503.
5. European Published Patent Application 0388962.
6. European Published Patent Application 0238011.
7. European Published Patent Application 0579955.

These references are pertinent to the factual determination of the level of ordinary skill in the pertinent art. These references are cited and discussed in applicants' specification or the International Search Report in applicants' corresponding International (PCT) patent applications.

Reconsideration, reexamination and allowance of the claims are requested

Respectfully submitted,

September 2, 2008
Date

Virgil H. Marsh
Virgil H. Marsh
Reg. No. 23,083

Fisher, Christen & Sabol
1725 K Street, NW
Suite 1108
Washington, D.C. 20006
Phone: 202-659-2000
Fax: 202-659-2015
E-mail: FCSabol@aol.com